

R E M A R K S

The claims are amended to require that the diuretic be an ENaC inhibitor. The two species of this type of diuretic, as claimed in the original claims, are amiloride and triamterene, which are now represented in separate dependent claims. This includes new claim 22 which is within the elected invention.

Although claims 8-20 were withdrawn from consideration as being non-elected, these are method of use claims which have been amended to require the pharmaceutical composition of the elected claims, and have been retained in the application for the possibility of their being rejoined.

The claims are rejected as being unpatentable over Hosokawa et al. and several additional articles. Claim 4 is rejected as being unpatentable over Hosokawa et al. in view of WO 97/31907 (cited as Willson et al).

Reconsideration of the rejection in view of the amendments made hereinabove and the following are respectfully requested.

With respect to the citation of the Willson et al. to show the preferred insulin sensitizer of claim 4, applicants request that if this position is maintained, the specific portion of

Willson et al. on which the Examiner is relying, be made of record. Applicants have advised that they are unable to find the statement relied upon by the Examiner in the Willson et al. document.

As to Hosokawa et al., the primarily cited reference, it is submitted that this is being cited only with hindsight of the present disclosure. Hosokawa states that the cause of edema, which is induced by troglitazone, is the alteration of intestinal ion transport (page 1080, ABSTRACT). Therefore, the author concluded that the reagents, which inhibit the alteration of intestinal ion transport, could be effective to treat edema. Acetazolamide is the example of the inhibitor of the alteration of intestinal ion transport, so it influenced the decrease in  $I_{sc}$  evoked by troglitazone (page 1082, Table 1).

However, regarding amiloride, the author said that it did not influence the decrease in  $I_{sc}$  evoked by troglitazone (page 1082, Table 1) because amiloride is NOT one of the inhibitors of the alteration of intestinal ion transport.

It is therefore submitted that, from the above, this document does not teach the combination effect of troglitazone and the diuretics which do NOT inhibit the alteration of

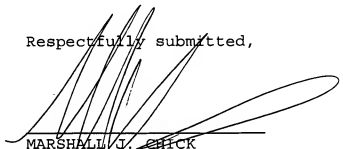
intestinal ion transport. Furthermore, there is no concrete evidence of the connection between  $I_{sc}$  value and treating edema in this document.

In addition to the above, it is submitted that Example 2 (Figure 2) of the present application shows an unexpected result in the combination effect of amiloride with compound A, thereby providing further support for the patentability of the present claim combination of ENaC inhibitors with insulin sensitizers.

In view of the above, entry of this AMENDMENT and allowance of the application are respectfully requested.

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Respectfully submitted,



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